The University of Michigan
Medical Center

Ann Arbor, Michigan 48109-0362

Department of Internal Medicine
Division of Gastroenterology
3912 Taubman Center
(313) 936-4780 (Office)
(313) 936-7392 (Fax)

747-2964

Council for Tobacco Research-USA, Inc.
900 Third Avenue
New York, New York 10022
(212) 421-8885

May 15, 1991

Dear Sirs,

I am writing to request a research grant from the Council for Tobacco Research. The Council is interested in funding projects which explore the pathogenesis of diseases associated with smoking such as cardiovascular disease, chronic lung disease and cancer. Another disease strongly associated with smoking but sometimes over shadowed by the above diseases is peptic ulcer disease. Besides being at increased risk for ulcers smokers with peptic ulcers have an eighty percent one year recurrence of their ulcer. They are also refractory to healing by the standard ulcer medications such as cimetidine and ranitidine and are also at a significantly higher risk of having a major complication from their ulcer such as bleeding or perforation. The reason for this increase in peptic ulcer disease is unknown.

The pathogenesis of peptic ulcer disease is still largely unknown. While higher than average gastric acid output is often seen in people with duodenal ulcers the opposite is seen in people with gastric ulcers and there is a great amount of overlap. So gastric acid may be necessary for ulcer formation but it is not considered to be the major etiologic factor in ulcer formation per se. This has led to the exploration of several other possible causes including mucosal blood flow, prostaglandins, bicarbonate secretion, helicobacter pylori and gastroduodenal motility. Dysfunction of normal gastroduodenal motility may play a major role in peptic ulcer disease because if normal motility is inhibited the exposure of gastric or duodenal mucosa to acid and pepsins will be increased and possibly lead to the break down of the mucosa.

Currently there is very little information on this topic. Gastric emptying studies have been done on smokers and nonsmokers to look for differences but only one study has been done while actually smoking and these results have been conflicting. We have designed a series of studies which record gastroduodenal motility and duodenal pH during smoking and nonsmoking sessions in smokers and nonsmokers. To better understand the mechanism behind any observed change in motility we also obtain serum levels of the hormones secretin and motilin in addition to duodenal pH. Our preliminary results on nine volunteers are fairly dramatic. All volunteers, smokers and nonsmokers, have complete loss of an important motility pattern called the phase III MMC or the "housekeeper" movement. The housekeeper movement is seen in all individuals about every 90 minutes and consists of strong contractions waves beginning in the stomach and then proceeding throughout the small intestine. The function of this movement is believed to be to clean out the lumin of the stomach and intestine of static secretions, sloughed mucosal cells or any foreign material remaining in the gut. All of are volunteers demonstrated normal motility patterns while not smoking and during the smoking period they all demonstrated complete loss of gastric phase III MMC activity but not duodenal phase III activity. All volunteers also demonstrated a dramatic fall in the normal gastric contraction activity which occurs between the phase III MMC. This is called the phase II MMC activity. We believe these findings are significant because they are marked changes in normal function and they have occurred in all volunteers to date. This work may lead to greater insight into the gastric morbidity associated with smoking. To date no other mechanism has been found linking

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smoking to peptic ulcer disease. People have looked at smocking's effect on gastric acid output, mucus production prostaglandin production etc. without results.

We believe that this information will be a major finding in the understanding of the pathophysiology of peptic ulcer disease associated with smoking and will be a major news event. I have enclosed an abstract of our work. I understand the purpose of this letter is to determine if you are interested in the over all concept of this work and if so we will submit a formal proposal with detailed preliminary data. While this work falls outside the usual cardiovascular-pulmonary-cancer axis that is traditionally associated with smoking studies we strongly urge you to consider supporting this work because it is an area that greatly effects millions of smokers.

Thank you for considering this proposal.

Sincerely, 313-747-2964

W. Michael McDonnell, MD
Instructor of Internal Medicine

Chung Owyang, MD
Professor of Internal Medicine
Chief, Division of Gastroenterology
6500 MSRB-I
1150 W. Medical Center Dr.
University of Michigan
Ann Arbor, MI 48109

Fax (313) 763-2535

PS. Please note that the enclosed Abstract won ~~the~~ the Clinical Science research competition at the national American College of Physicians meeting in 1990

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